TARGETED THERAPY IN CANCER

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ABSTRACT
Cancer is one of the most common causes of death, taking nearly 7 million lives each year worldwide. New cancer targeted therapies that make use of therapeutic antibodies and small molecules have made treatment more tumor specific and less toxic. To meet the present challenges in cancer, the most promising way is targeted therapy that may be used to make targeting more specific the cancerous cells.

KEY WORDS: Targeted therapy, Therapeutic antibodies, Small molecules, cancerous cells.

INTRODUCTION
Targeted therapy refers to a new generation of cancer drugs designed to interfere with a specific target protein that is believed to have a critical role in tumor growth or progression. This approach contrasts with the conventional cytotoxic chemotherapeutics that have been used in major cancer therapy in past decades. The molecular identification of cancer antigens has opened new possibilities for the development of effective immunotherapy, antibody therapy and ligand targeted therapy is a successful means of improving the selective toxicity of anti cancer therapy.

TYPES OF TARGETED THERAPY
Two types of drugs that can be used as targeted therapies,

- Small molecules
- Monoclonal Antibodies

Each of these drug types has distinct characteristics that have important biological and clinical implications.
Small Molecules (Receptor targeted)

Many targeted therapies are small molecules. Once in the body, most small molecules can easily travel across cell membranes, including the plasma membrane. This means that they can be used to interfere with proteins located either outside or inside the cell. Small molecules are often designed to interact with specific areas of the target protein in order to modify its enzyme activity or its interaction with other molecules.

Gleevec (imatinib) is one example of a small-molecule targeted therapy that inhibits a few key signaling pathways.

(Mechanism of imatinib is illustrated in fig. no.1)

1. EGFR inhibitors
2. Angiogenesis inhibitors
3. Proteasome Inhibitors
4. Immunotherapy
5. Other Agents: non-HER Tyrosine Kinase Inhibitors
6. Tyrosine Kinase Inhibitors:

EGFR: Tyrosine Kinase Inhibitors

A tyrosine kinase receptor is a molecular structure on the surface of a cell that binds with substances such as hormones, antigens, drugs, or neurotransmitters. When it binds with one of these triggering substances, the receptor performs a chemical reaction, which in turn triggers a series of reactions inside the cell. These reactions include cell multiplication, death, maturation, and migration. In tumor cells, all of these reactions are critical for the tumor to survive, thrive and spread throughout the body. By blocking the receptor, the goal is to prevent the cascade of reactions and prevent tumor survival.

One family of tyrosine kinase receptors is called the human epidermal receptor family, or the HER family. The members of the family are:

HER1 (also called the Epidermal Growth Factor Receptor or EGFR)
HER2 (also called ErbB2)
HER3 (also called ErbB3)
HER4 (also called ErbB4)

The first 2 family members, EGFR and HER2, are the two most extensively studied targets in oncology.
EGFR inhibitors
Within this group, there are two types of inhibitors, small molecule inhibitors and antibody inhibitors.
EGFR inhibitors are illustrated in table 1

HER2 inhibitors
HER2 inhibitors are illustrated in table 2

Bcr-abl inhibitors
Another group of tyrosine kinase inhibitors inhibit the bcr-abl tyrosine kinase, which is formed in certain types of leukemia.
Bcr-abl inhibitors are illustrated in table 3

There are three main anti-EGFR drugs:
- Gefitinib
- Erlotinib
- Cetuximab.

I) Gefitinib

Structure 1: Gefitinib

Gefitinib is an oral medication that acts as a small molecule EGFR inhibitor.

Side Effects of Gefitinib-
The most common side effects associated with gefitinib (250 mg) are as follows:
- Diarrhoea (48%)
- Rash (43%)
- Acne, dry skin (25%, 13%)
- Nausea and/or vomiting (25%)
II) Erlotinib

![Erlotinib Structure]

Studies of erlotinib are underway in other solid tumors, including ovarian, colorectal, head and neck, renal cell carcinoma, glioma and gastrointestinal cancer.

Side Effects of Erlotinib-
- Diarrhea seen with a 200-mg dose
- Headache
- Nausea/vomiting

Serious Side Effects-
- Infusion reactions (3%)
- Interstitial lung disease (0.5%)
- Sepsis (3%)
- Kidney dysfunction (2%)

Angiogenesis Inhibitors
New blood vessel formation is called angiogenesis, and the proteins that trigger this process are called pro-angiogenic factors. The main pro-angiogenic factor is VEGF, which stands for vascular endothelial growth factor. In essence, by secreting VEGF and other related proteins to stimulate new blood vessel growth, tumors support and feed themselves, allowing them to grow. The concept behind angiogenesis inhibition, then, is to thwart this process and thereby fight tumor progression.

Angiogenesis inhibitors are illustrated in table no.4

I) Bevacizumab
Bevacizumab is a targeted therapy against the vascular endothelial growth factor (VEGF), a signaling protein that leads to the birth of new blood vessels, \textit{i.e.} vascular growth. Like cetuximab and trastuzumab, bevacizumab is a monoclonal antibody that binds to its specific
target, in this case VEGF.

Endothelial cells are the cells that line the insides of blood vessels; they contain receptors which bind VEGF. In the presence of VEGF-binding, these endothelial cells multiply and new blood vessels are formed. Active tumors secrete VEGF because they need more blood supply in order to get nutrients to maintain their growth. By blocking VEGF, bevacizumab prevents the interaction of VEGF with its receptors on the surface of endothelial cells.

Side Effects of Bevacizumab-
- Weakness
- Abdominal pain
- Deep vein thrombosis (clot)
- High blood pressure
- Fainting
- Diarrhea

Serious Side Effects-
- Formation of holes in the colon (gastrointestinal perforation), generally requiring surgery and sometimes leading to intra-abdominal infections

PROTEASOME INHIBITOR
The proteasome is a structure inside the cell, which breaks down proteins that have been labeled to undergo degradation and recycling.

By binding part of the proteasome, a drug can inhibit the breakdown of some of these proteins that have been marked for destruction. This "wreaks havoc" in a sense, and can result in growth arrest or death of the cell. In fact, and fortunately, this tends to happen more so in cancer cells than in normal cells.

Proteasome inhibitors are illustrated in table 5
Bortezomib

Structure 3: Bortezomib

Bortezomib is the first drug in the proteasome inhibitor class of anti-cancer agents & used in the treatment of multiple myeloma which is a hematologic cancer.

Side Effects of Bortezomib-
- Fatigue, malaise, weakness – 65%
- Nausea – 64%
- Diarrhea – 51%
- Weight loss/ decreased appetite – 43%
- Low platelet counts – 43%
- Peripheral neuropathy - 37%

IMMUNOTHERAPY

Targeted immunotherapy agents bind to their targets, not to interfere with growth signals, but rather to trigger immune signals. By binding specific protein particles (antigens) that are found on the surface certain types of cancer cells, targeted immunotherapy agents can lead to a series of anti-tumor immune reactions in the body, ultimately causing the tumor cell to die. Furthermore, if these immunotherapy drugs are chemically attached to radioactive substances, you could launch a dual attack on the tumor cells, taking advantage of both the anti-tumor immune response and the anti-tumor radiation reaction.

Targeted immunotherapy drugs are essentially a collection of monoclonal antibodies, all of which have different targets. Antibodies are proteins that seek out and bind to specific antigens; every antibody has a particular antigen with which it "fits". Antibodies are named for the antigen that they bind, e.g.: the anti-CD20 antibody binds to the antigen CD20. The term monoclonal means that a group of antibodies all came from one master cell. Immunotherapeutic agents are illustrated in table 6

It includes three main drugs,
- Rituximab
- Tositumomab
- Ibritumomab

Rituximab

Rituximab targets the CD-20 protein found on the surface of normal and cancerous B-cells.
(B-cells are a part of the immune system that helps make antibodies). About 85% of all non-Hodgkin’s lymphomas (NHLs) are of the B-cell type (the other 15% are T-cell type). Of the B-cell NHLs, more than 90% express the CD-20 target. Thus, rituximab is used in patients with CD20-positive non-Hodgkin’s lymphoma (NHL).

**Side Effects of Rituximab**

Some of the main side effects of rituximab are infusion-related reactions.

The most common infusion-related symptoms include:

- Fever – 53%
- Chills/rigors – 33%
- Nausea – 23%
- Weakness – 26%

**Other Types**

Other types of drugs are illustrated in table 6

1) **Imatinib mesylate**

![Structure 4: Ematinib](image)

**Side Effects of Imatinib Mesylate**

Side effects frequently reported in trials include:

- Nausea
- Vomiting
- Edema (fluid retention)
- Muscle cramps
- Heartburn
TYROSINE KINASE INHIBITORS: Her-2
Tyrosine Kinase Inhibitor is an important class of targeted therapies. There are three main EGFR inhibitors. Major Her2 targeted drug i.e. trastuzumab, or Herceptin is a TK inhibitor.

TRASTUZUMAB
Trastuzumab targets cancer cells that "overexpress," or make too much of HER–2, a protein which is found on the surface of cancer cells. Like cetuximab, trastuzumab is a monoclonal antibody that targets the extracellular portion of a receptor, in this case the HER-2 receptor (as opposed to the EGF receptor for cetuximab). By doing so, it slows or stops the growth of these cells, but only for cancers that overexpress Her-2, such as breast cancer.

Side Effects of Trastuzumab-
The main side effects of Trastuzumab during the first treatment are:
• Fever and/or chills
• Pain
• Weakness
• Nausea, vomiting and headache.

Serious Side Effects-
• damage to heart muscle that can lead to heart failure
  o symptoms include shortness of breath, difficulty breathing, fast or irregular heartbeat, increased cough, and swelling of the feet or lower legs
• damage to the lungs, causing severe or life-threatening breathing problems that require immediate medical attention
• allergic reactions that can be severe or life-threatening with drop in blood pressure, shortness of breath, rashes, and wheezing.

Monoclonal Antibodies
The interaction of signaling molecules with receptors on the outside of a cell often activates pathways inside the cell. Monoclonal antibodies can interfere with these signaling pathways in cancer cells in a number of ways:
First, antibodies can work outside the cell by preventing signaling molecules and receptors from interacting with each other. (Mechanism of monoclonal antibody is illustrated in fig. no.2 a)
They can also be used as delivery vehicles, guiding radioactive molecules or toxins to the cancer cells. (Mechanism of monoclonal antibody is illustrated in fig. no. 2 b)

Third, antibodies attached to a cell can trigger an immune response that destroys the cell. (Mechanism of monoclonal antibody is illustrated in fig. no. 2c)

Herceptin (trastuzumab), Bevacizumab, Tositumomab, Mylotarg, and rituximab are examples of monoclonal antibodies used to treat cancer.

Examples of licensed monoclonal antibodies include:

- Rituximab targets CD20 found on B cells. It is used in non Hodgkin lymphoma
- Trastuzumab targets the ErbB2 receptor expressed in some types of breast cancer
- Cetuximab targets the epidermal growth factor receptor. It is used in the treatment of colon cancer and non-small cell lung cancer.

Bevacizumab targets circulating VEGF ligand. It is approved for use in the treatment of colon cancer, breast cancer, non-small cell lung cancer, and is investigational in the treatment of sarcoma. Its use for the treatment of brain tumors has been recommended.

**Immuonconjugate**

Immuonconjugates are antibodies conjugated to a second molecule, usually a toxin, radioisototope or label. These conjugates are used in immunotherapy and to develop monoclonal antibody therapy as a targeted form of chemotherapy.

**Types of Monoclonal Antibody**

I. Murine,
II. Chimeric,
III. Humanized monoclonal antibody
IV. Human.

Example of FDA Approved Therapeutic Monoclonal Antibodies are illustrated in table 7

**Radio immunotherapy (RIT)**

Radioimmunotherapy involves the use of radioactively conjugated murine antibodies against cellular antigens. Most research currently involved their application to lymphomas, as these are highly radio-sensitive malignancies. To limit radiation exposure, murine antibodies were especially chosen, as their high immunogenicity promotes rapid clearance from the body. Tositumomab is an exemplar used for non-Hodgkins lymphoma.
Antibody-Directed Enzyme Prodrug Therapy (ADEPT)
ADEPT involves the application of cancer associated monoclonal antibodies which are linked to a drug-activating enzyme. Subsequent systemic administration of a non-toxic agent results in its conversion to a toxic drug, and resulting in a cytotoxic effect which can be targeted at malignant cells. The clinical success of ADEPT treatments has been limited to date. However it holds great promise and recent reports suggest that it will have a role in future oncological treatment.

Drug and Gene Therapy: Immuno-Liposomes
Immunoliposomes are antibody-conjugated liposomes. Liposomes can carry drugs or therapeutic nucleotides and when conjugated with monoclonal antibodies, may be directed against malignant cells. Although this technique is still in its infancy, significant advances have been made. Immunoliposomes have been successfully used in vivo to achieve targeted delivery of tumor-suppressing genes into tumors, using an antibody fragment against the human transferrin receptor. Tissue-specific gene delivery using immunoliposomes has also been achieved in brain, and breast cancer tissue.

TARGETED THERAPIES VS CHEMOTHERAPY
Difference Between Chemotherapy And Targeted Therapy is illustrated in fig. no. 3
Targeted therapies are different because:

- They act on specific molecular targets that have been identified through research, while most standard chemotherapies act on all rapidly dividing cells.
- They are deliberately chosen or designed to interact with their target, while many standard chemotherapies were identified through trial and error.
  Also, targeted therapies may be associated with fewer and less toxic side effects than standard chemotherapy, since they may cause less damage to normal cells.

Biology of Targeted Therapy
Mechanism of traditional therapy is illustrated in fig. no.4
Traditional cytotoxic chemotherapy works primarily through the inhibition of cell division (figure 4). In addition to cancer cells, other rapidly dividing cells (e.g., hair, gastrointestinal epithelium, etc.) are affected by these drugs. In contrast, targeted therapy blocks the proliferation of cancer cells by interfering with specific molecules required for tumor development and growth (figure 5) some of these molecules may be present in normal
tissues, but they are often mutated or overexpressed in tumors. Among the earliest targeted therapies were antibodies directed against the cell surface markers cluster of differentiation 20 (CD20), CD33, and CD52, which are present on lymphoma and leukemia cells. Because CD20 is also present on normal lymphoid cells, targeting of this molecule affects overall immune function.

**Mechanisms of traditional chemotherapy** (refer fig 4)

These drugs act on rapidly dividing cells, which include normal tissues (e.g., hair, gastrointestinal epithelium, bone marrow) in addition to cancer cells. Alkylating agents interfere with DNA base pairing, leading to strand breaks and arresting DNA replication. Topoisomerase inhibitors prevent DNA uncoiling. Taxanes and vinca alkaloids interfere with micro-tubule function required for cell mitosis. Antimetabolites block the formation and use of nucleic acids essential for DNA replication.

The molecular pathways most often targeted in the treatment of solid tumors (e.g., breast, lung, and colorectal cancers) are those of the epidermal growth factor receptor (EGFR, also known as HER1), vascular endothelial growth factor (VEGF), and HER2 (Figure 2). Such pathways can be inhibited at multiple levels: by binding and neutralizing ligands (i.e., molecules that bind to specific receptor sites on cells); by occupying receptor-binding sites (thereby preventing ligand binding); by blocking receptor signaling within the cancer cell; or by interfering with downstream intra-cellular molecules. Monoclonal antibodies, which are usually water soluble and large (typical molecular weight of approximately 150,000 Da), target extracellular components of these pathways, such as ligands and receptor-binding domains. In contrast, small molecule inhibitors (typical molecular weight of approximately 500 Da) can enter cells, thereby blocking receptor signaling and interfering with downstream intracellular molecules.

**Mechanisms of targeted therapies** (refer fig 5)

The molecular targets in this figure are not overexpressed in a single cell type, but rather on various malignant and normal tissues. For example, CD20 is present on lymphoma and normal lymphoid cells, HER2 is present on 25 percent of breast cancer cells, and VEGFR is present on normal and tumor-associated vasculature. Downstream intracellular signaling molecules, some of which are targeted by small molecule inhibitors, are not depicted. Some drugs (e.g., sorafenib [Nexavar], sunitinib [Sutent], imatinib [Gleevec], dasatinib [Sprycel]) have multiple targets, most of which are not depicted. (CD = cluster of differentiation; BCR-
ABL = breakpoint cluster region-Abelson; EGFR = epithelial growth factor receptor; VEGFR = vascular endothelial growth factor receptor; VEGF = vascular endothelial growth factor.)

EGFR, which is present in multiple tumor types, contributes to cancer cell proliferation, invasion, and migration because EGFR is also present in normal epithelial tissue (i.e., skin and mucosa), EGFR inhibition can lead to significant dermatologic (Figure 4) and gastrointestinal toxicities. In many cases the development of a rash seems to indicate that the treatment may be working.\cite{4,5,6} In severe cases, dermatologic toxicity may require discontinuation of the EGFR inhibitor and implementation of measures such as topical or systemic antibiotics, topical retinoid, or topical steroids.\cite{7} Additionally, up to 50 percent of patients taking EGFR inhibitors develop diarrhea. For most patients, this toxicity is self-limited and responds to symptomatic treatment, such as loperamide (Imodium). Occasionally, severe diarrhea may result in significant volume loss and may require administration of parenteral fluids.

Side effects caused due to EGFR inhibition is illustrated in fig. no. 6

Acne form rash on (A) the face and (B) back of patients treated with cetuximab (Erbitux), a monoclonal antibody targeting epidermal growth factor receptor.

**IMPLICATIONS OF TARGETED THERAPY**

The use of targeted therapy has markedly changed outcomes for some diseases. Imatinib has had a dramatic effect on chronic myeloid leukemia, and rituximab, sunitinib, and trastuzumab have revolutionized the treatment of non-Hodgkin's lymphoma, renal cell carcinoma, and breast cancer, respectively. In other instances, the degree of clinical benefit is more modest. In patients with advanced pancreatic cancer, the addition of erlotinib to standard chemotherapy increases the one-year survival rate from 17 to 24 percent, which correlates to an increase in median survival from 24 to 27 weeks.\cite{8}

**ILLUSTRATIONS**

Table no. 1: EGFR Inhibitos

<table>
<thead>
<tr>
<th>Small Molecule inhibitors</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Lab Development Name</th>
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<tr>
<td>Iressa</td>
<td>Gefitinib</td>
<td>ZD1839</td>
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<td>Tarceva</td>
<td>Erlotinib</td>
<td>OSI 771</td>
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<table>
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<th>Antibody inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Erbitux</td>
<td>Cetuximab</td>
<td>C225</td>
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Table no. 2: HER2 inhibitors

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<th>Lab Development Name</th>
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<td>Herceptin</td>
<td>Trastuzumab</td>
<td>NO 34</td>
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<tr>
<td>Tykerb</td>
<td>Lapatinib</td>
<td>GW572016</td>
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* this drug targets HER2/neu and EGFR

Table no. 3: Bcr-abl inhibitors

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<th>Brand Name</th>
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<td>Dasatinib</td>
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<td>STI 571</td>
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Table no 4: Angiogenesis inhibitors

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</thead>
<tbody>
<tr>
<td>Avastin</td>
<td>Bevacizumab</td>
<td>anti-VEGF</td>
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Table 5: Proteasome inhibitors

<table>
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<th>Lab Development Name</th>
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</thead>
<tbody>
<tr>
<td>Velcade</td>
<td>Bortezomib</td>
<td>PS-341</td>
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</table>

Table 6: other types of drugs

<table>
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<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Lab Development Name</th>
</tr>
</thead>
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<tr>
<td>Gleevec</td>
<td>Imatinib</td>
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<tr>
<td>Gleevec</td>
<td>Imatinib</td>
<td>mesylate</td>
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Table 7: List of FDA approved monoclonal an antibodies

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Approval date</th>
<th>Type</th>
<th>Target</th>
<th>Approved treatment(s)</th>
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<tbody>
<tr>
<td>ReoPro</td>
<td>1994</td>
<td>Chimeric</td>
<td>inhibition of glycoprotein IIb/IIIa</td>
<td>Cardiovascular disease</td>
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<tr>
<td>Humira</td>
<td>2002</td>
<td>Human</td>
<td>inhibition of TNF-α signaling</td>
<td>Several auto-immune disorders</td>
</tr>
</tbody>
</table>
• FIGURES

Fig. no. 1. Mechanism of imatinib

Fig no. 2(a). Mechanism of monoclonal antibody

Fig. no. 2(b). Mechanism of monoclonal antibody
Fig. no. 2(c). Mechanism of monoclonal antibody

Fig. no. 3 Difference between chemotherapy and targeted therapy

Fig. no. 4 Mechanism of Traditional therapy
CONCLUSION
Targeted therapies are very important drugs in the treatment of different cancers, alone or in combination with classical cytotoxic agents. This class of drugs inhibits specific target in tumor cells or in the tumor micro environment, explaining their generally favorable toxicity profile, with limited effects on bone marrow and intestinal epithelium. However, it is important to analyze the biologic effects of targeted therapy in cancer cells as well as in normal tissues. Many of adverse events related to these agents have been described only after more prolonged use, such as the case of cardiac toxicity due to trastuzumab. In fact, very few side effects can be linked to the mechanism of action of the drugs themselves.

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